

B. REMARKS

Claims 60-79 stand rejected under 35 U.S.C. 102(e) as being anticipated by Johnstone, et al., U.S. Patent No. 5,908,784, as evidenced by the Cellgro catalog, the U.S. Biological Catalog (2004), and Williams, et al. This rejection is respectfully traversed.

The U.S. Biological Catalogue was published in 2004, and Williams was published in 2003, and the Cellgro catalog was published on October 6, 2001. The above-identified application was filed on June 4, 1999, which is a Section 371 application of PCT Application No. PCT/US97/22022, filed December 5, 1997, which claims priority based on provisional application Serial No. 60/035,274, filed December 6, 1996.

The Examiner relies upon Ex parte Erlich, 22 U.S.P.Q. 1463 (Bd. App. Int. 1992), to justify his reliance on the Cellgro catalog, the U.S. Biological Catalog (2004), and Williams in that the Examiner states that, in accordance with Erlich, these references show the level of ordinary skill in the art at or around the time the invention was made, even though such references postdate the claimed invention.

Erlich holds, however, that in order for a reference which was published after the filing date of an application to be relied upon to show the level of ordinary skill of the art at the time of the claimed invention, it must state clearly what the level of ordinary skill in the art was at the time the invention was made. In Erlich, the Applicant established a date of completion of his invention of June 12, 1980. The Board held that a reference, published in July 1981, could be relied upon in a rejection under 35 U.S.C. 103 because the reference cited other references dated 1979 and 1980 which showed the level of ordinary skill in the art at that time. (Erlich, at 1464-1465.)

The U.S. Biological Catalog (2004) and the Cellgro catalog provide no information as to the level of ordinary skill in the art as of June 4, 1999, the filing date of the above-identified application, or as of the December 5, 1997 filing date of Applicants' PCT Application No. PCT/US97/22022, or as of the December 6, 1996 filing date of Applicants' provisional application Serial No. 60/035,274. Therefore, pursuant to Erlich, the U.S. Biological Catalog

(2004) and the Cellgro catalog are not prior art against the above-identified application, and the rejection under 35 U.S.C. 102(e) will be addressed with respect only to Johnstone and Williams.

The Federal Circuit has held that anticipation is established only if all elements of an invention, as stated in a patent claim, are identically set forth in a single prior art reference. All of the limitations must be disclosed by the reference either expressly or inherently. (See *Mehl/Biophile International Corp. v. Milgraum*, 192 F.3d 1362 (Fed. Cir. 1999) at 1365; 52 U.S.P.Q.2d 1303, at 1306; *Oney v. Ratliff*, 182 F.3d 893 (Fed. Cir. 1999); 51 U.S.P.Q.2d 1697; *Finnigan Corp. v. U.S. International Trade Commission*, 180 F.3d 1354 (Fed. Cir. 1999), at 1367; 51 U.S.P.Q.2d 1001, at 1009; *General Electric Co. v. Nintendo Co., Ltd.*, 179 F.3d 1350 (Fed. Cir. 1999), at 1356, 50 U.S.P.Q.2d 1910, at 1915.) Anticipation is a question of fact. (*Rockwell International Corp. v. United States*, 147 F.3d 1358 (Fed. Cir. 1998), at 1363; 47 U.S.P.Q.2d 1027, at 1031.)

Johnstone does not disclose or even remotely suggest to one of ordinary skill in the art a chondrogenic medium that includes a simple sugar in an amount of from about 3g/l to about 7g/l. The only specific concentration of glucose disclosed by Johnstone is 1g/l, which is in a medium known as Dulbecco's Modified Eagle's Medium-Low Glucose (DMEM-LG). Although, at Column 4, lines 31 and 32, Johnstone lists "Dulbecco's Modified Eagle's Medium (DMEM)," as an example of a medium which may be used to promote chondrogenesis of mesenchymal stem cells, DMEM does not inherently have a simple sugar concentration of from 3g/l to 7g/l. In fact, Johnstone discloses, and Examiner even admits at Page 3, lines 1-4 of the Final Rejection, that there are examples of DMEM that have a glucose concentration of only 1g/l, including the DMEM used specifically by Johnstone. Therefore, all of the limitations of Claims 60-79 are not disclosed, either expressly or inherently, by Johnstone.

In fact, contrary to the requirements for anticipation under 35 U.S.C. 102, the Examiner relies on an additional reference, Williams, in order to formulate the rejection. Williams, at Page 680, column 1, refers to Rosen, et al., *J. Bone Miner. Res.*, Vol. 9, pg. 1759 (1994), Johnstone, et al., *Exp. Cell Res.*, Vol. 238, pg. 265 (1998), and Mackay, et al., *Tissue Eng.*, Vol. 4, pg. 415 (1998) to show that bone morphogenic protein 2, TGF- β_1 or TGF- β_3 can induce mesenchymal cells to differentiate into chondrocytes.

Firstly, the Johnstone and Mackay papers were published in 1998, after the filing dates of Applicants' provisional and PCT applications and, therefore, are not prior art.

The Rosen paper is directed to the use of bone morphogenic protein 2(BMP-2) for differentiating clonal limb bud cells into cartilage or bone. Nothing Rosen discloses or even remotely suggests to one of ordinary skill in the art a medium for producing chondrocytes from mesenchymal stem cells which includes, in addition to a chondroinductive agent, a chemically defined minimum essential medium, ascorbate or an analog thereof, an iron source, insulin or an insulin-like growth factor, and a simple sugar present in an amount of from about 3 g/l to about 7 g/l.

Thus, even the combination of Johnstone and Williams does not disclose all of the elements of Applicants' Claims 60-79, either expressly or inherently. In addition, the combination of Johnstone and Williams does not even remotely suggest to one of ordinary skill in the art that a culture medium having a simple sugar concentration from 3g/l to 7g/l may be used as part of a culture medium for mesenchymal stem cells for enabling the mesenchymal stem cells to differentiate into chondrocytes. Therefore, Johnstone does not anticipate Applicants' processes as claimed, nor does Johnstone render Applicants' processes as claimed obvious to one of ordinary skill in the art. It is therefore respectfully requested that the rejection under 35 U.S.C. 102(e) be reconsidered and withdrawn.

Claims 60-99 stand rejected under 35 U.S.C. 103 as being unpatentable over Johnstone, et al, U.S. Patent No. 5,908,784, in view of Hunziker, U.S. Patent No. 5,368,858, as evidenced by the Cellgro catalog, the U.S. Biological Catalog, and Williams. This rejection is respectfully traversed.

As noted hereinabove, the U.S. Biological Catalog and the Cellgro catalog are not effective prior art references. Therefore, the rejection under 35 U.S.C. 103 will be addressed only with respect to Johnstone, Hunziker, and Williams.

The differences between Johnstone and Applicants' claimed processes have been noted hereinabove. Johnstone clearly does not disclose or even remotely suggest Applicants' claimed processes to one of ordinary skill in the art.

The Examiner relies on Hunziker to show that TGF- β 3 may be used in a composition for transforming repair cells into chondrocytes. Hunziker discloses the treatment and repair of defects or lesions in cartilage by filling the defect or lesion with a biodegradable matrix containing a proliferation agent, a transforming agent, and repair cells. TGF- β , including TGF- β 3, may be used as a proliferation agent and/or as a transforming factor. Insulin-like growth factor also may be used as a proliferation agent.

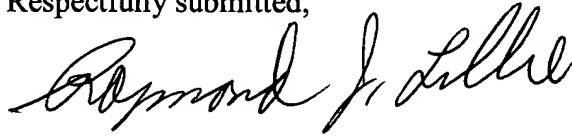
The composition of Hunziker, however, does not include a chemically defined minimal essential medium, ascorbate or an analog thereof, an iron source, and a simple sugar present in an amount of from 3g/l to 7g/l. Hunziker also does not even remotely suggest to one of ordinary skill in the art to include such components. Hunziker, therefore, does not disclose or even remotely suggest to one of ordinary skill in the art Applicants' processes as claimed. Thus, Hunziker does not render Applicants' processes as claimed obvious to one of ordinary skill in the art.

The combination of Johnstone, Hunziker, and Williams does not disclose or even remotely suggest to one of ordinary skill in the art a process for producing mesenchymal stem cells wherein the mesenchymal stem cells are cultured in a medium which includes all of the components claimed by Applicants, including a simple sugar which is present in the medium in an amount of from 3g/l to 7g/l. Applicants and only Applicants have discovered that by culturing mesenchymal stem cells in a chondrogenic medium which includes a simple sugar at a concentration of from about 3g/l to about 7g/l, one obtains improved differentiation of mesenchymal stem cells into chondrocytes as opposed to media which have a lower sugar concentration, such as, for example, media which have a glucose concentration which is the standard concentration present in "low glucose DMEM" (1g/l). At best, the combination of Johnstone, Hunziker, and Williams would suggest to one of ordinary skill in the art to supply a chondrogenic medium which includes glucose at a concentration of only 1g/l. Johnstone, Hunziker, and the Williams, therefore, did not contemplate Applicants' improvement for

producing chondrocytes from mesenchymal stem cells wherein there is included in the chondrogenic medium a simple sugar which is present in the medium in an amount of from about 3g/l to about 7g/l. Therefore, the combination of Johnstone, Hunziker, and Williams does not render Applicants' process as claimed obvious to one of ordinary skill in the art, and it is therefore respectfully requested that the rejection under 35 U.S.C. 103 be reconsidered and withdrawn.

For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejections be reconsidered and withdrawn and a favorable action is hereby solicited.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Raymond J. Lillie". The signature is fluid and cursive, with the first name being the most prominent.

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